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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/389,782	09/03/99	DUNSTAN C	A-604

EXAMINER	
HELMS, L	
ART UNIT	PAPER NUMBER
1642	11

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/389,782	Dunstan et al
Examiner	**Group Art Unit**
Larry R. Helms Ph.D.	1642

☒ Responsive to communication(s) filed on *25 Jan 2001*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-20* is/are pending in the applicat

Of the above, claim(s) *8-17, 19, and 20* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-7 and 18* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☒ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 6 + 10

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

☒ NOTICE TO COMPLY WITH SEQUENCE REQUIREMENTS

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Applicant's election of Group I, claims 1-7 and 18 in Paper No. 9 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 8-17 and 19-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions. Election was made **without** traverse in Paper No. 9.

3. Claims 1-7 and 18 are under examination.

Specification

4. The disclosure is objected to because of the following informalities:

The specification of page 14, for example needs to include the SEQ ID Nos for peptides encompassed by the sequence rules..

Appropriate correction is required.

Sequence Requirements

5. In order to advance prosecution an action on the merits could be performed even though this application is not in sequence compliance (see page 14 of specification). This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Any questions regarding compliance with the sequence rules requirements specifically should be directed to the departments listed at the bottom of the Notice to Comply.

APPLICANT IS GIVEN THE TIME LIMIT ALLOTTED IN THIS LETTER WITHIN WHICH TO COMPLY WITH THE SEQUENCE RULES, 37 C.R.F. §§ 1.821-1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R. § 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. § 1.136. In no case may an applicant extend the period for response beyond the six month statutory period. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.

Claim Objections

6. Claims 3 and 6 are objected to because of the following informalities:

a. Claim 3 needs to have "SEQ ID NO:1" inserted after "Figure 1" in line 5 of the claim. Claim 6 should contain SEQ ID Nos for the sequences encompassed by the sequence rules. Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-6 and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-6 and 18 are indefinite because they contain the abbreviation "OPG" in claims 1 and 4. Full terminology should be in first instance of the claims followed by the abbreviation in parentheses. Dependent claims may then use the abbreviation. Abbreviations render the claim indefinite because the same abbreviation may represent more than one element or concept.

b. Claim 18 is indefinite for reciting "an effective amount". The phrase "an effective amount" is indefinite when the claims fails to state the function which is to be achieve. In re Frederiksen, 213 F 2d 547, 102 USPQ 35 (CCPA 1954).

c. Claims 1-4 are indefinite for reciting "variant" and "derivative" in claims 1, 3, and 4 because the meaning of the terms are not clear. The terms "derivative" and "variant" are not one which has a universally accepted meaning in the art nor is it one which has been adequately defined in the specification in terms of functional meaning. The primary deficiency in the use of this phrase is the absence of a ascertainable meaning for said phrase. Since it is unclear how the proteins are to be derivatized to yield the class of derivatives referred to in the claims, there is no way for a person of skill in the art to ascribe a discrete and identifiable class of compounds to said phrase. Further, it is not clear whether the "derivative" of the protein is formed by attachment of a detectable marker, therapeutic molecule, some other molecule or altering the amino acid sequence, for examples. In addition, since the term "derivative" does not appear to be clearly defined in the specification, and the term can encompass proteins with amino acid substitutions, insertions, or deletions, chemically derivatized molecules, or even mimetics. In absence of a single defined art recognized meaning for the phrase and lacking a definition of the term in the specification, one of skill in the art could not determine the metes and bounds of the claims.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a fusion protein comprising a OPG polypeptide with a FC protein wherein the amino acid sequence is SEQ ID NO5, 6, 7, or 8 and conjugates to water soluble polymers and compositions comprising such, does not reasonably provide enablement for a fusion protein comprising any FC or OPG fragment, variant or derivative with any number of deletions or substitutions, wherein the protein does not retain a biological activity of OPG in inhibiting bone resorption and the Fc protein does not provide longer half life or protein A binding, or Fc receptor binding, or complement fixation, or placental transfer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to any variant, fragment, or derivative of a Fc protein or a OPG protein wherein the fusion protein does not retain the biological activity of the Fc region or the OPG protein. The claims encompass any number of deletions and substitutions that alter the Fc protein which would alter its usefulness to increase plasma half life. The claims broadly read on pharmaceutical compositions comprising such fusion proteins.

The specification teaches OPG is a protein that is a potent factor in blocking bone resorption (see page 2, line 34-35). The specification teaches fusion proteins comprising OPG and Fc (see page 15, lines 25-35) and water soluble polymers conjugated to such. The specification teaches fusion proteins with SEQ ID Nos 3-8 retain in vivo activity (see Example 2). The specification does not enable any variant, fragment, or derivative or any number of substitutions, or deletions in the Fc or the OPG protein such that the fusion protein does not retain a biological activity as listed above for the OPG and the Fc protein.

The claims are not commensurate in scope with the enablement provided in the specification. Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, the replacement of a single lysine at position 118 of the acidic fibroblast growth factor by a glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al, Journal of Cell Biology Vol 111 November 1990 2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with asparagine, did not affect biological activity while the replacement with serine

or glutamic acid sharply reduced the biological activity of the mitogen (see Lazar et al Molecular and Cellular Biology Mar 1988 Vol 8 No 3 1247-1252).

Replacement of the histidine at position 10 of the B-chain of human insulin with aspartic acid converts the molecule into a superagonist with 5 times the activity of nature human insulin. Schwartz et al, Proc Natl Acad Sci USA Vol 84:6408-6411 (1987). Removal of the amino terminal histidine of glucagon substantially decreases the ability of the molecule to bind to its receptor and activate adenylate cyclase. Lin et al Biochemistry USA Vol 14:1559-1563 (1975).

These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of the protein.

Although biotechnology has made great strides in the recent past, these references serve to demonstrate exactly how little we really know about the art. Elucidation of the genetic code induces one to believe that one can readily obtain a functional synthetic protein for any known nucleic acid sequence with predictable results. The results of the construction of synthetic proteins remain very unpredictable as Burgess et al, Lazar et al, Schwartz et al, and Lin et al conclusively demonstrate.

In view of the lack of guidance, lack of examples, and lack of predictability associated with regard to producing and using the myriad of derivatives encompassed in the scope of the claims, one skilled in the art would be forced into undue experimentation in order to practice the broadly claimed invention.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

12. Claims 1 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Boyle et al (WO 97/23614, published 7/3/97, IDS #6).

a. The claims recite a protein having a formula of R1-R2 wherein R1 is Fc and R2 is OPG, wherein the OPG amino acid sequence is from 22-185 to 401.

b. Boyle et la teach a fusion protein comprising OPG [22-201] -Fc (see entire document, especially page 16, line 6).

13. Claim 1 is rejected under 35 U.S.C. 102(e) as being anticipated by Boyle et al (U.S. Patent 6,015,938, filed 11/18/97 which is a divisional which has a filing date of 12/22/95).

a. Claim 1 has been described supra.

b. Boyle et al teach a fusion protein comprising Fc and OPG (see column 7, line 63).

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 1-7 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mann et al (WO 98/28427, published 7/2/98, IDS #6) and further in view of Boyle et al (U.S. Patent 6,015,938, filed as a divisional with a filing date of 12/22/95).

Claims 1 and 4 have been described supra. Claims 2, 3, 5, 6, 7, and 18 recite wherein the protein has the formula R2-L-R1, the Fc protein is SEQ ID NO:1, the linker is $(Gly)_7$ and wherein the fusion protein is SEQ ID NO:5, 6, 7, or 8.

Mann et al teach fusion proteins comprising the Fc of SEQ ID NO:1 (see SEQ ID NO:9) and modifications to ablate the Fc receptor binding or complement binding (see page 8, lines 23-25) and many linkers, specifically the linker (Gly)7 (see page 9, lines 10-23) and polymers conjugated to proteins and pharmaceutical compositions comprising such (see pages 15-31). Mann et al also teach the advantages of Fc fusions to proteins in general (see page 2-3) and the fusions of many proteins to Fc proteins (see pages 3-4). Mann et al does not specifically teach the OPG protein or the specific sequences of SEQ ID NO 5, 6, 7, or 8. This deficiency is made up for in the teachings of Boyle et al.

Boyle et al teach the OPG protein and fusion proteins comprising the Fc protein and OPG (see entire document, specifically column 7, line 58 to column 8, line 26). Boyle et al also teach conjugation to soluble polymers (see column 8, lines 34-45). Boyle et al also teach the OPG can

be from residues 22 to any of residues 180-410 (see column 7-8) and pharmaceutical compositions.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the OPG protein as taught by Boyle et al and produce a fusion protein with the Fc protein with a linker as taught by Mann et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the OPG protein as taught by Boyle et al and produce a fusion protein with the Fc protein with a linker as taught by Mann et al because Boyle et al specifically teaches fusion proteins of OPG to Fc wherein the OPG can comprise residues 22 to 180-401. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the OPG protein as taught by Boyle et al and produce a fusion protein with the Fc protein with a linker as taught by Mann et al because Mann et al teach fusion proteins of Fc and many therapeutically important proteins to achieve increased circulation times and Mann et al also teach modifications to the Fc protein to ablate certain functions and fusions with a linker. It would have been obvious to substitute any therapeutically important protein such as OPG for the OB protein of Mann et al given the teachings in Boyle et al that OPG is therapeutically important for bone resorption. It would also be obvious to produce the fusion protein as R2-L-R1 because Boyle et al teach modifications at the N or C-terminal of OPG and as such one skilled in the art would conclude that any orientation would be expected to work. In addition, it would be obvious that a fusion protein of OPG and Fc with modifications as

taught by Mann et al for a Fc protein and modifications as taught by Boyle et al for OPG would have the sequences recited in claim 7.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusions

17. No claims are allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

19. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official

Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879

SHEELA HUFF
PRIMARY EXAMINER